PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 44.35.79247/001	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/GB 03/05607	International filing date *(day/month/year)* 22.12.2003	Priority date *(day/month/year)* 20.12.2002
International Patent Classification (IPC) or both national classification and IPC G01N33/68		
Applicant AXIS-SHIELD ASA et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
28.05.2004	31.01.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer GONCALVES M L F C Telephone No. +49 89 2399-8127

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB 03/05607

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-46 as originally filed

Claims, Numbers

1-27 as originally filed

Drawings, Sheets

1/7-7/7 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 10-13

   because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 10-13

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees, the applicant has:

   ☐ restricted the claims.

   ☒ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☐ all parts.

☒ the parts relating to claims Nos. 1-9,14-27 .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-9, 14-27
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-9, 14-27
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-9, 14-27
	No:	Claims	

2. Citations and explanations

see separate sheet

The following documents were cited in the search report:

D1: L BLOOD, W.B. SAUNDERS, PHILADELPHIA, VA, US, vol. 79, 1992, pages 1907-1915,

D2: WO 00/11479

D3: US-A-5 455 160

D4: US-A-4 833 074

D5: FEMS IMMUNOLOGY AND MEDICAL MICROBIOLOGY. NETHERLANDS SEP 2000, vol. 29, no. 1, September 2000, pages 27-33,

D6: US-A-5 776 348

D7: JOURNAL OF CLINICAL PERIODONTOLOGY, COPENHAGEN, DK, vol. 26, no. 10, 1999, pages 653-657,

D8: EUROPEAN JOURNAL OF CARDIO-THORACIC SURGERY, SPRINGER VERLAG, BERLIN, DE, vol. 5, no. 7, 1991, pages 363-367,

D9: WO 98/20355 A

D10: US 2002/168784 A1

D11 :SCANDINAVIAN JOURNAL OF THORACIC AND CARDIOVASCULAR SURGERY, STOCKHOLM, SE, vol. 30, no. 2, 1996, pages 53-59,

D12 :GRANULOCYTE AND COMPLEMENT ACTIVATION" PERFUSION, vol. 9, no. 2, March 1994, pages 109-117,

D13 :SCANDINAVIAN JOURNAL OF IMMUNOLOGY, BLACKWELL SCIENCE PUBL., OXFORD, GB, vol. 40, no. 6, December 1994, pages 675-680,

1. The claims 10 to 13 relate to subject-matter in respect of which no international search report has been established and thus need not be subject of an international preliminary examination (Rule 66.1(e) PCT).

2. This International Preliminary Examining Authority found multiple (groups of) inventions in this international application, as follows:

   1. Claims: 1-9 assay method for the detection of potential or propensity for cardiovascular disease

   2. Claims: 14-27, assay method for the determination of calprotectin in a body fluid by turbidimetry; kit and automated apparatus therefor; methods of diagnostic using the turbidimetric assay method.

   The Sets of claims 1 and 2 have in common that they involve measuring

calprotectin.

Methods for the measurement of calprotectin are however known, for example, from document US 4833074, cited in the application,(see claims). Thus these common features of the sets of claims D1 not provide a single general inventive concept linking the claims.

The subject-matter of claims 1-9 in essence differs from that known from document US 4833074 in that the measured calprotectin is used as a marker for potential for or propensity for cardiovascular disease. The problem addressed in these claims im view of document US 4833074 is to provide a method of determining susceptibility to cardiovascular disease before the onset of the symptoms. This problem is addressed by measuring the level of calprotectin in various body fluids, an abnormally high calprotectin level being indicative of susceptibility to cardiovascular disease.

The subject-matter of claims 14-27 in essence differs from that known from document US 4833074 in that calprotectin is measured by use of a turbidimetric or "particle based" immunoassay instead of an enzyme immunoassay. The problem addressed in these claims im view of document US 4833074 is the improvement of the measurement of calprotectin. This problem is addressed by use of a turbidimetric or "particle based" immunoassay, which is a sensitive technique that allows both the determination of low concentrations of calprotectin and the accurate measurement of relative high concentrations of calprotectin. This type of assay is quick and easy to perform, when compared to the prior art, and may also be automated.

The above analysis demonstrates that the subject-matter of the two groups of claims is also not linked by providing a solution to a common problem.

In conclusion neither the technical features in common to the groups of claims nor the problem solved by each of the two groups of claims provides a corresponding special technical feature, which establishes a single general inventive concept linking any of the two sets of claims. Thus the technical relationship between the subject-matter of the sets of claims is lacking, and the requirement for unity of invention referred to in Rule 13.1 PCT is not fulfilled.

3. The subject-matter of claim 1 is assay method for the detection of potential or propensity for cardiovascular disease.

The subject-matter of claim 1 in essence differs from that known from document WO0011479 in that the measured calprotectin is used as a marker for potential for or propensity for cardiovascular disease (instead of assessment of the concentration of holo transcobalin from document WO0011479). The problem addressed in these claims im view of document WO0011479 is to provide a method of determining susceptibility to cardiovascular disease before the onset of the symptoms. This problem is addressed by measuring the level of calprotectin in various body fluids, an abnormally high calprotectin level being indicative of susceptibility to cardiovascular disease.

The assay of claim 1 is based on **the finding that the protein calprotectin is a useful marker or indicator of potential for CVD or propensity to CDV before the onset of the symptoms**. Such a finding is not anticipated by any disclosures in the known prior art documents, thus the subject-matter of claim 1 is novel (Article 33 (2) PCT).

The fact that calprotectin is a useful marker or indicator of potential for CVD even before the onset of the symptoms cannot be derived from the known prior art documents, either taken alone or in combination. This finding also allows for the provision of **a method of determining susceptibility to cardiovascular disease before the onset of the symptoms.** Due to this unexpected effect, the presence of an inventive step can be acknowledged (Article 33 (3) PCT).

4. Dependent claims 2 to 9 add features to the assay of claim 1 and thus also relate to novel and inventive subject-matter (Article 33 (2) and (3) PCT).

5. The subject-matter of claims 14 is an assay method for the determination of calprotectin in calprotectin containing body fluid. The subject-matter of claim 14, in essence differs from that known from document US 4833074 in that calprotectin is measured by use of a turbidimetric or "particle based" immunoassay instead of an enzyme immunoassay. The problem addressed in the method of claim 14 im view of document US 4833074 is the improvement of the measurement of calprotectin. This problem is addressed by use of a turbidimetric or "particle based" immunoassay, which is a sensitive technique and has the unexpected effect that **allows both the determination of low concentrations of calprotectin and the accurate measurement of relative high concentrations of calprotectin**. This type of assay is **quick and easy to perform**, when compared to the prior art, and **may also be automated.**

The turbidimetric or "particle based" immunoassay of claim 14 for the determination of calprotectin, is not known from the prior art documents cited in the search report, which refer all to other enzyme immunoassays The turbidimetric or "particle based" immunoassay of claim 14 for the determination of calprotectin cannot be derived from the prior art documents cited in the search report, either taking the documents alone or in combination.

Thus, the assay method for the determination of calprotectin in calprotectin containing body fluid of claim 14 is novel and based on an inventive concept (Article 33 (2) and (3) PCT).

6. Dependent claims 15 to 19 add features to the method of claim 14 and thus also relate to novel and inventive subject-matter (Article 33 (2) and (3) PCT).

7. The above comments (see item 5) also apply to the subject-matter of independent claims 20 (referring to a kit for use as a diagnostic assay according to the method of claim 14); 25 (an automated apparatus to perform the assay according to the method of claim 14); 26 (a method of diagnosis comprising the determination of calprotectin in calprotectin-containing body fluid according to the method of claim 14) and to the claims dependent thereon (Article 33 (2) and (3) PCT)